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Expedited Articles

Discovery and Synthesis of (*S*)-3-[2-(3,4-Dimethoxyphenyl)ethoxy]-2-(4,6-dimethylpyrimidin-2-yloxy)-3,3-diphenylpropionic Acid (LU 302872), a Novel Orally Active Mixed ET_A/ET_B Receptor Antagonist

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Structural variation of the endothelin A-selective antagonist (*S*)-3-methoxy-2-(4,6-dimethoxypyrimidin-2-yloxy)-3,3-diphenylpropionic acid (LU 135252) led to analogues which retain ET_A affinity but exhibit substantial ET_B affinity as well. The most active derivative obtained is (*S*)-3-[2-(3,4-dimethoxyphenyl)ethoxy]-2-(4,6-dimethylpyrimidin-2-yloxy)-3,3-diphenylpropionic acid (LU 302872), which can be prepared in enantiomerically pure form in eight steps via an acid-catalyzed transetherification. It has a $K_i = 2.15$ nM for binding to the ET_A receptor and a $K_i = 4.75$ nM for binding to the ET_B receptor, is orally available, and antagonizes the big ET-induced blood pressure increase in rats and the big ET-induced bronchospasm in guinea pigs each time at a dose of 10 mg/kg.

Introduction

Endothelins (ET) are a family of 21 amino acid peptides (ET-1, ET-2, ET-3)[1] which act as modulators of the vascular tone, cell proliferation, and hormone production.[2] Their actions are mediated by two receptors, the ET_A and the ET_B receptor, which are seven transmembrane domain receptors that couple to different intracellular signaling pathways via heterotrimeric G proteins. Due to their pronounced physiological effects and because elevated levels of ET-1 have been found in a number of disease states, ET is considered to be relevant in the pathogenesis of several diseases such as myocardial infarction,[3] hypertension,[4] congestive heart failure,[5] atherosclerosis,[6] cerebral vasospasm,[7] renal failure,[8] asthma,[9] and prostate hyperplasia.[10] With regard to the different localizations and functions of ET receptor subtypes, it might be beneficial to block specifically only one receptor or both receptors at the same time.[11]

Meanwhile, a number of potent balanced ET receptor antagonists has been reported including SB-209670,[12] L-749,329,[13] and A-182086.[14] All these compounds strongly depend on the presence of a benzodioxole moiety which in other cases has been shown to be metabolically unstable.[15] Other balanced antagonists are Bosentan (Ro 47-0203)[16] and Ro 48-5695[17] belonging to a group of sulfonamides and IRL 3461[18] which might be considered as peptidic.

In the present article we report the discovery of a novel class of nonpeptidic mixed ET_A/ET_B receptor antagonists.

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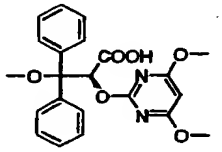
Chemistry

SAR studies in the development of the selective ET_A antagonist (*S*)-3-methoxy-2-(4,6-dimethoxypyrimidin-2-yloxy)-3,3-diphenylpropionic acid LU 135252 (**1**, active enantiomer of LU 127043[19]) demonstrated the impor-



LU 135252 (1)
K_i (ET_A) = 1.4 nM, K_i (ET_B) = 184 nM

tance of the substituent in the β-position. If the methoxy group was replaced by a more lipophilic side chain containing a phenyl group, the ET_B affinity was improved substantially whereas the ET_A affinity was essentially retained. The general synthesis of these compounds is shown in Scheme 1. A detailed protocol describing the preparation of **4** has been published previously.[19] The hydroxy ester **4** is hydrolyzed by KOH to produce the carboxylic acid **5** in over 90% yield. Conversion of **5** to the dianion and reaction with an appropriate pyrimidine derivative gives the final product **6** in up to 80% yield. As indicated in Scheme 1, this short sequence allows a broad variation of the core structure.

The desired endothelin receptor antagonists have been prepared in enantiomerically pure form by optical resolution of compounds **5** or **6** in several cases, but this strategy sometimes gave poor results which was particularly true for the preparation of the hydroxy carboxylic acid (*S*)-**10**. This problem was solved by a three-

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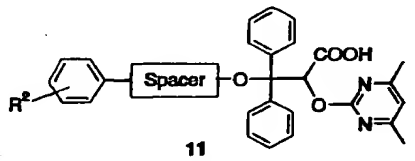
Table 1. Effect of a Spacer between a Phenyl Group and an Oxygen Atom in β-Position



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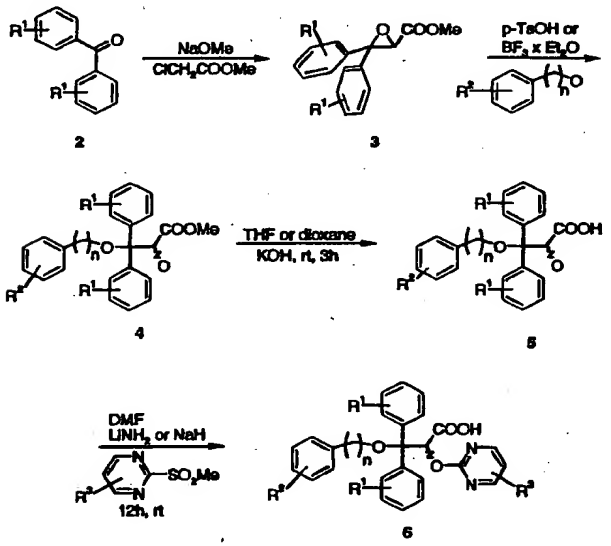
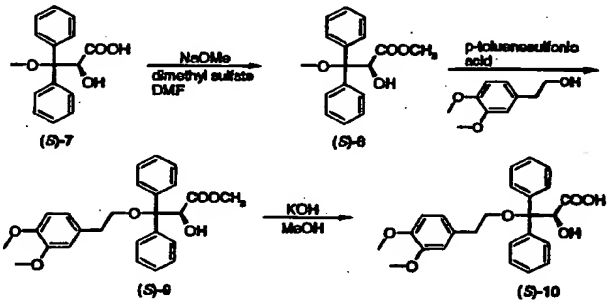
compd	spacer	R^2	K_i (nM)[a] ET_A	K_i (nM)[a] ET_B	A/B ratio
11a	CH_2-CH_2	4-Me	32.5	55	1.7
11b	CH_2-CH_2-CH_2	4-Me	23	170	7.4
11c	CH=CH-CH_2	4-Me	32	320	10
11d	CH_2-CH_2	3,4,5-TriOMe	1.38 ± 0.2	3.21 ± 0.19	2.3
11e	CH=CH-CH_2	3,4,5-TriOMe	48	20	0.4
11f		3,4-DiOMe	0.48 ± 0.09	60	125
11g	CH_2	3,4-DiOMe	2	63	31
11h	CH_2-CH_2	3,4-DiOMe	3.49 ± 0.75	7.15 ± 0.63	2.0
(*S*)-**11h** (LU 302872)	CH_2-CH_2	3,4-DiOMe	2.15 ± 0.66	4.75 ± 0.57	2.2

[a] K_i's ± SE were determined from the inhibition of [^{125}I]ET-1 (ET_A assay) or [^{125}I]ET-3 (ET_B assay) binding to cloned human ET_A or ET_B receptor as described in the Experimental Section.

Scheme 1. General Synthesis of the Endothelin Receptor Antagonists



Scheme 2. Synthesis of Enantiomerically Pure Hydroxy Acid (*S*)-**10**



step procedure (Scheme 2): the (*S*)-hydroxy acid **7** (ee > 99%), already used in large quantities for the preparation of **1**, is first converted to the methyl ester (*S*)-**8**. Then, the methoxy group is replaced by 2-(3,4-dimethoxyphenyl)ethanol in an acid-catalyzed transetherification without loss of enantiomeric purity. The resulting methyl ester (*S*)-**9** is finally hydrolyzed to the hydroxy carboxylic acid (*S*)-**10** with an ee of >99%. This threest p synthesis can be performed without purification of intermediates in an overall yield of 60% on a kilogram scale.

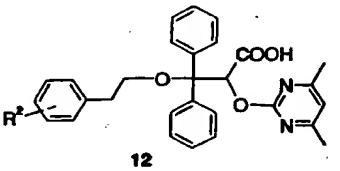
Results and Discussion

SAR studies for the novel balanced receptor antagonists are summarized in Tables 1−3. As shown in Table 1, it was possible to substantially improve ET_B affinity through modification of the spacer between the β-oxygen atom and the aromatic group. The length of this alkyl chain, varying from zero to three carbon atoms, was found to have a much stronger influence over ET_B affinity than over the ET_A binding. With regard t th ET_A/ET_B ratio and the receptor affinity, the optimal chain length seems to be 2 carbon atoms as incorp ration of a C-1 or a C-3 spacer already resulted in a decrease in binding affinity toward the ET_B recept r.

Table 2 highlights the effect of the substituent at the phenyl ring. A methyl group or a sterically equivalent chlorine atom in the para position afforded compounds with a balanced antagonism, but with a low affinity for both receptors. Introduction of alkoxy substituents improved markedly the binding activity which was particularly pronounced for compounds **11d** and **11h**. A free hydroxy group instead of a methoxy group is tolerated (**12e**), whereas the introduction of a carboxylic acid in the para position (**12g**) surprisingly resulted in an almost selective ET_A antagonist.

Once the spacer length and the substitution pattern of the phenyl group of the side chain were established, compounds **12a** and **11h** were taken for further variations of R^1 and R^3. Introduction of a substituted phenyl ring in the β-position afforded compounds with an ET_A/ET_B ratio of 1 or even less, but it was unfortunately accompanied by a substantial loss of binding affinity to both receptors. This result matches the findings of the previously reported ET_A selective antagonist **1**.[19] On the contrary, variation of R^3 gave no clear SAR. Replacement of one methyl group in **11h** by a methoxy group (**13e**) gave a compound with an inferior ET_A/ET_B ratio, but reverse cases were also found (not shown in the

Table 2. Effect of the Variation of R^2 on the Binding Affinity



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compd	R^2	K_i (nM)[a] ET_A	K_i (nM)[a] ET_B	A/B ratio
11a	4-Me	32.5	55	1.7
11d	3,4,5-TriOMe	1.38 ± 0.75	3.21 ± 0.19	2.3
11h	3,4-DiOMe	3.49 ± 0.75	7.15 ± 0.63	2.0
12a	4-OMe	6.03 ± 0.89	24.2 ± 6.1	4.0
12b	4-Cl	19.8 ± 3.5	94.1 ± 18.5	4.7
12c	3-OMe, 4-OEt	3.13 ± 0.66	25.1 ± 6.6	8.0
12d	H	25	230	9.2
12e	4-OH	3.48 ± 1.21	16.2 ± 3.4	4.7
12f	3-OMe, 4-OCH_2COOH	1.92 ± 0.92	24	12
12g	4-COOH	1.5	115	77

[a] K_i's ± SE were determined from the inhibition of [^{125}I]ET-1 (ET_A assay) or [^{125}I]ET-3 (ET_B assay) binding to cloned human ET_A or ET_B receptor as described in the Experimental Section.

table). Fortunately, the 4,6-dimethylpyrimidine that gave the best results (Table 3) is most easily synthesized as well.

As several compounds showed a good binding profile t both receptors, functional ET-1 antagonism was examined in vivo to assess their oral bioavailability. The results for the big ET-1 induced blood pressure increase in rats (ET_A antagonism) are summarized in Table 4.[10] Two compounds, **12c** and **11h**, showed a very pronounced effect, which is even equal to our selective ET_A antagonist **1**. On the contrary, identical doses of Bosentan (Roche) did not show any activity under the same conditions. The weak effect of **12f** might be explained by its higher polarity. Compound **11h** was chosen for further evaluation because it showed a better affinity t the ET_B receptor; in addition the corresponding phenethyl alcohol is easier to synthesize than the alcohol necessary for **12c**.

To demonstrate the ET_B antagonism and the effectiveness in a second species as well, compound **11h** was tested for inhibition of big ET 1-induced bronchospasm in guinea pigs. The results are summarized in Table 5. Two hours after treatment with 10 mg/kg p.o. of compound (*S*)-**11h** (LU 302872) or its racemate **11h**, a very strong protection (79% and 67%, respectively) against bronchospasm was observed. This effect could not be achieved with the ET_A-selective antagonist **1** even using 30 mg/kg p.o.

Compound **11h** was synthesized in both enantiomeric forms which show K_i values of 2.15 and 73 nM, respectively, for the ET_A receptor and 4.75 and 170 nM, respectively, for the ET_B receptor. The biologically active enantiomer should have the (*S*)-configuration, as the (*S*)-enantiomer of **5** was used for its preparation. The bioavailability of (*S*)-**11h** was determined to be 50−70% in dog.

Experimental Secti n

Receptor Binding Studies. The binding studies were performed using CHO cells stably expressing human ET_A or ET_B receptors. Membrane protein (10−50 μg) was incubated for 30 min at 25 °C in 50 mM Tris-HCl, pH 7.4, containing 5 mM $MnCl_2$, 40 μg/mL bacitracin, and 0.2% BSA, with 25 pM [^{125}I]ET-1 (ET_A assay) or 25 pM [^{125}I]ET-3 (ET_B assay) in the presence or absence of the test compound. Nonspecific binding was measured with 0.1 μM ET-1. All assays were performed in triplicate and repeated at least once.

After incubation, membranes were collected on GF/B glass fiber filters and radioactivity was determined by liquid scintillation counting.

Evaluation. The specific radioligand binding to each receptor was defined as the difference between total binding and nonspecific binding determined in the presence of an excess of unlabeled ligand (ET-1, 10^{-7} M). K_i values were determined either from IC_{50} values according to Cheng and Prusoff (for determinations based on three concentrations of test compound) or by nonlinear regression analysis using a program similar to LIGAND.[20,21] Standard errors were determined by simultaneous fitting of two or three repeated inhibition curves.

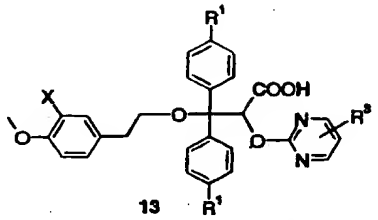
Oral Activity in Rats and Guinea Pigs. Inhibition of ET-Induced Blood Pressure Increase in Rats. The ET antagonists were given orally in a dose of 10 mg/kg to male Sprague−Dawley rats. The animals were anesthetized with urethane (1.6 g/kg i.p.) and tracheotomized 90 min later. The left carotid artery was cannulated for blood pressure determination and the left jugular vein for administration of big ET-1. Next, 120 min after oral administration of the ET antagonists, 20 μg/kg big ET-1 was given i.v.[22] Blood pressure was recorded over 30 min, and the area under the data (AUD_{30min}) was calculated.

Inhibition of ET-Induced Bronchospasm in Guinea Pigs. Bronchospasm was investigated using a modification of Konzett's and Rössler's method.[23,24] Male guinea pigs (Dunkin Hartley, Harlan) weighing 300−450 g were orally treated with the ET antagonists and were anesthetized with pentobarbital (60 mg/kg i.p.) 90 min later. The animals were artificially ventilated using a Starling pump with an inspiratory pressure of 100 mm H_2O, a tidal volume of 5 mL/100 g body weight, and 60 strokes/min. Excess air not taken up by the lungs was bypassed. Respiratory volume (mL) was measured as the pressure difference using a whole body plethysmograph and a Fleisch tube. At 120 min after oral treatment with ET antagonists, the anesthetized guinea pigs received an i.v. injection of 20 μg/kg big ET-1. This induces a long lasting bronchospasm, as indicated by the reduction of respiratory volume, which was monitored over 30 min, followed by calculation of the area under the data (AUD_{30min}).

General Chemical Procedures. Unless otherwise specified, all solvents and reagents were obtained from commercial suppliers and used without further purification. Synthesis of substituted benzophenones is described in ref 19. Melting points were determined with a Büchi 530 apparatus and are uncorrected. Analytical TLC was performed on silica gel plates (Merck silica gel 60 F_{254}). All final products were shown to be homogeneous by gradient HPLC on a HP 1090 liquid chromatograph with UV detection. ^{1}H NMR spectra were recorded using Bruker DPX200 (200 MHz), Bruker AC250 (250 MHz), or Bruker AC270 (270 MHz) spectrometers. All values are reported as chemical shifts in δ units (ppm) relative to tetramethylsilane as internal standard. Mass spectral analysis was accomplished with a Finnigan MAT 90 instrument using direct chemical ionization techniques, or a Micromass Q-TOF for high-resolution MS (HRMS). Optical rotation was determined on a Perkin-Elmer 241 polarimeter. The following abbreviations are used in the Experimental Section: DMF, dimethylformamide; NaOMe, sodium methoxide; THF, tetrahydrofuran.

3-[2-(3,4-Dimethoxyphenyl)ethoxy]-2-[(4,6-dimethylpyrimidin-2-yl)oxy]-3,3-diphenylpropionic Acid (11h). (a) 3-[2-(3,4-Dimethoxyphenyl)ethoxy]-2-hydroxy-3,3-diphenylpropionic Acid Methyl Ester. A solution of 3,3-diphenyloxirane-2-carboxylic acid methyl ester[19] (7.00 g; 27.5 mmol) and 2-(3,4-dimethoxyphenyl)ethanol (5.50 g; 30.2 mmol) in dichloromethane (20 mL) was treated with boron trifluoride etherate (5 drops) at room temperature and subsequently

Table 3. Effect of the Variation of R^1 and R^3 on the Binding Affinity



compd	R^1	X	R^3	K_i (nM)[a] ET_A	K_i (nM)[a] ET_B	A/B ratio
12a	H	H	4,6-DiMe	6.3 ± 0.89	24.2 ± 6.1	3.8
13a	H	H	4-OMe, 6-Me	1.95 ± 0.53	23.2 ± 3.9	11.8
13b	Me	H	4-OMe, 5,6-$(CH_2)_2$-O-	105 ± 25	71.2 ± 11.4	0.7
13c	ethyl	H	4,6-DiMe	250	195	0.8
13d	ethyl	H	4-OMe, 6-Me	155	160	1
11h	H	OMe	4,6-DiMe	3.49 ± 0.75	7.15 ± 0.63	2.0
13e	H	OMe	4-OMe, 6-Me	2.37 ± 0.48	14.7 ± 1.7	6.2
13f	Cl	OMe	4-OMe, 6-Me	230	130	0.6
13g	Cl	OMe	4-OMe, 5,6-$(CH_2)_3$	290	215	0.7
13h	ethyl	OMe	4-OMe, 6-Me	39.3 ± 8.9	40 ± 2.3	1

[a] K_i's ± SE were determined from the inhibition of [^{125}I]ET-1 (ET_A assay) or [^{125}I]ET-3 (ET_B assay) binding to cloned human ET_A or ET_B receptor as described in the Experimental Section.

Table 4. Inhibition of Big ET-Induced Blood Pressure Increase in Rats with LU 135252 and Balanced $ET_{A/B}$ Receptor Antagonists[a]

compd	BP increase (AUD_{30min})[b] [mmHg × min] control	drug-treated	% reduction
12a	1464 ± 89	976 ± 121	33 ± 8
12c	1464 ± 89	475 ± 218[c]	68 ± 15[c]
12f	1476 ± 117	1294 ± 456	14 ± 31
11d	1487 ± 113	1123 ± 176	25 ± 12
11h	1507 ± 86	641 ± 120[c]	58 ± 8[c]
(*S*)-**11h**	1507 ± 86	583 ± 140[c]	61 ± 9[c]
Bosentan	1507 ± 86	1399 ± 92	7 ± 6
LU 135252	1507 ± 86	636 ± 178[c]	58 ± 12[c]

[a] 10 mg/kg p.o., 2 h pretreatment. [b] All values reported as mean ± SEM. [c] $p < 0.05$ vs control.

Table 5. Inhibition of Big ET-Induced Bronchospasm in Guinea Pigs with LU 135252 and Balanced $ET_{A/B}$ Receptor Antagonists[a]

compd	reduction in respiratory volume AUD_{30min}[b] [mL × min] control	drug-treated	% inhibition
11h	213 ± 41	71 ± 16[c]	67 ± 8[c]
(*S*)-**11h**	213 ± 41	46 ± 15[c]	79 ± 7[c]
LU 135252	213 ± 41	172 ± 26[d]	19 ± 12

[a] 10 mg/kg p.o., 2 h pretreatment. [b] All values reported as mean ± SEM. [c] $p < 0.05$ vs control. [d] 30 mg/kg p.o.

stirred for 2 h. The solvent was evaporated, and the crude residue (10.7 g; 89%) was used without further purification.

(b) 3-[2-(3,4-Dimethoxyphenyl)ethoxy]-2-hydroxy-3,3-diphenylpropionic Acid. 3-(2-(3,4-Dimethoxyphenyl)ethoxy)-2-hydroxy-3,3-diphenylpropionic acid methyl ester (12.0 g; 27.5 mmol) was dissolved in dioxane (110 mL), followed by treatment with 1 N NaOH (55 mL). The resulting mixture was stirred at 80 °C for 2 h. After cooling to room temperature, the reaction mixture was diluted with water and extracted with ether (2×). The aqueous layer was acidified with 1 N HCl and extracted with ether again. The organic layer was dried over magnesium sulfate and the solvent was evaporated. The crude residue was crystallized from diethyl ether/*n*-hexane to yield the desired carboxylic acid as colorless crystals (10.2 g; 87%): ^{1}H NMR ($CDCl_3$, 270 MHz) δ 7.4−7.1 (10 H, m), 6.8 (1 H, d), 6.7 (1 H, dbr), 6.6 (1 H, sbr), 5.0 (1 H, s), 3.9 (3 H, s), 3.85 (3 H, s), 3.6 (1 H, dt), 3.4 (1 H, OH), 3.2 (1 H, dt), 2.8 (2 H, t); mp 92−93 °C.

(c) 11h. To a slurry of lithium amide (9.00 g; 390 mmol) in DMF (35 mL) was added a solution of 3-(2-(3,4-dimethoxyphenyl)ethoxy)-2-hydroxy-3,3-diphenylpropionic acid (55.0 g; 130 mmol) in DMF (150 mL) over a period of 15 min after which 2-methylsulfonyl-4,6-dimethylpyrimidine (25.0 g; 137 mmol), dissolved in DMF (75 mL), was added slowly. The resulting mixture was stirred at room temperature for 18 h; then, the reaction product was poured into ice/water (2 L), followed by acidification with citric acid. The precipitate was isolated by suction, washed with water, and while still moist, dissolved in dichloromethane. The solution of the crude product was dried over magnesium sulfate and evaporated to give an oily residue which was dissolved in ether. The ethereal solution was extracted with 1 N NaOH (130 mL); the aqueous layer was neutralized with 1 N HCl (130 mL) which resulted in the formation of a crystalline precipitate. After the precipitate dried, the pure product (64 g) was obtained: ^{1}H NMR ($CDCl_3$, 250 MHz) δ 7.3 (10 H, m), 6.7 (4 H, m), 6.3 (1 H, s), 3.9 (3 H, s), 3.85 (3 H, s), 3.75 (1 H, m), 3.6 (1 H, m), 2.8 (2 H, t), 2.3 (6 H, s); mass spectra 529 $(M + H)^+$; mp 125−130 °C. Anal. ($C_{31}H_{32}N_2O_6$) see (*S*)-**11h**.

3-[2-(4-Methylphenyl)ethoxy]-2-[(4,6-dimethylpyrimidin-2-yl)oxy]-3,3-diphenylpropionic Acid (11a). Compound **11a** was synthesized as described for **11h** using 2-(4-methylphenyl)ethanol in the first step: ^{1}H NMR ($CDCl_3$, 200 MHz) δ 7.3 (10 H, m), 7.0 (4 H, m), 6.7 (1 H, s), 6.3 (1 H, s), 3.7 (1 H, m), 3.5 (1 H, m), 2.8 (2 H, t), 2.3 (6 H, s), 2,25 (3 H, s); mp foam. HRMS calcd, 483.2282; found, 483.2271 $[M + H]^+$.

3-[3-(4-Methylphenyl)propoxy]-2-[(4,6-dimethylpyrimidin-2-yl)oxy]-3,3-diphenylpropionic Acid (11b). Compound **11b** was synthesized as described for **11h** using 3-(4-methylphenyl)propanol in the first step: ^{1}H NMR (DMSO-d_6, 270 MHz) δ 7.4−7.1 (10 H, m), 7.05 (4 H, m), 6.9 (1 H, m), 6.2 (1 H, s), 3.7 (1 H, m), 3.55 (1 H, m), 2.7 (2 H, t), 2.3 (6 H, s), 2.2 (1 H, m), 1.8 (2 H, m); mp 163−167 °C (dec). HRMS calcd, 497.2438; found, 497.2431 $[M + H]^+$. Anal. ($C_{31}H_{32}N_2O_4$) C, H, N.

3-[3-(4-Methylphenyl)prop-(2*E*)-enoxy]-2-[(4,6-dimethylpyrimidin-2-yl)oxy]-3,3-diphenylpropionic Acid (11c). Compound **11c** was synthesized as described for **11h** using 3-(4-methylphenyl)prop-(2*E*)-enol in the first step: ^{1}H NMR ($CDCl_3$, 200 MHz) δ 7.5−7.0 (14 H, m), 6.7 (1 H, s), 6.6 (1 H, d), 6.4 (1 H, s), 6.2 (1 H, dt), 4.3 (1 H, dd), 4.1 (1 H, dd), 2.35 (6 H, s), 2.3 (3 H, s); mp 181−182 °C. HRMS calcd, 495.2282; found, 495.2281 $[M + H]^+$.

3-[2-(3,4,5-Trimethoxyphenyl)ethoxy]-2-[(4,6-dimethylpyrimidin-2-yl)oxy]-3,3-diphenylpropionic Acid (11d). Compound **11d** was synthesized as described for **11h** using 2-(3,4,5-trimethoxyphenyl)ethanol in the first step: ^{1}H NMR ($CDCl_3$, 200 MHz) δ 7.3−7.1 (10 H, m), 6.7 (1 H, s), 6.35 (2 H, s), 6.3 (2 H, s), 3.9 (9 H, m), 3.8 (1 H, m), 3.6 (1 H, m), 2.8 (2 H, t), 2.3 (6 H, s); mp 154−155 °C. HRMS calcd, 559.2442; found, 559.2426 $[M + H]^+$.

3-[3-(3,4,5-Trimethoxyphenyl)prop-(2*E*)-enoxy]-2-[(4,6-dimethylpyrimidin-2-yl)oxy]-3,3-diphenylpropionic Acid (11e). Compound **11e** was synthesized as described for **11h** using 3-(3,4,5-trimethylphenyl)prop-(2*E*)-enol in the first step: ^{1}H NMR ($CDCl_3$, 200 MHz) δ 7.5−7.2 (10 H, m), 6.8 (1 H, m), 6.55 (1H, s), 6.5 (1 H, d), 6.3 (1 H, s), 6.15 (1 H, dt), 4.3 (1 H, dd), 4.1 (1 H, dd), 3.9 (6 H, s), 3.85 (3 H, s), 2.3 (6 H, s); mass spectra 571 $(M + H)^+$; mp foam.

3-(3,4-Dimethoxyphenoxy)-2-[(4,6-dimethylpyrimidin-2-yl)oxy]-3,3-diphenylpropionic Acid (11f). Compound **11f** was synthesized as described for **11h** using 3,4-dimethoxyphenol in the first step: ^{1}H NMR ($CDCl_3$, 200 MHz) δ 7.75 (2 H, m), 7.4−7.1 (8 H, m), 6.7 (1 H, m), 6.55 (2 H, m), 6.45 (1 H, dd); 6.2 (1 H, d), 3.8 (3 H, s), 3.6 (3 H, s), 2.3 (6 H, s); mp 115−116 °C. HRMS calcd, 501.2024; found, 501.2029 $[M + H]^+$. Anal. ($C_{33}H_{34}N_2O_7$) C, N; H calcd, 5.6; found, 6.1.

3-(3,4-Dimethoxybenzyloxy)-2-[(4,6-dimethylpyrimidin-2-yl)oxy]-3,3-diphenylpropionic Acid (11g). Compound **11g** was synthesized as described for **11h** using 3,4-dimethoxybenzyl alcohol in the first step: ^{1}H NMR ($CDCl_3$, 200 MHz) δ 7.5−7.2 (10 H, m), 6.95−6.8 (3 H, m), 6.7 (1 H, s); 6.3 (1 H, s), 4.6 (1 H, d), 4.5 (1 H, d), 3.85 (3 H, s), 3.8 (3 H, s), 2.3 (6 H, s); mp 125−126 °C. HRMS calcd, 515.2180; found, 515.2159 $[M + H]^+$.

3-[2-(4-Methoxyphenyl)ethoxy]-2-[(4,6-dimethylpyrimidin-2-yl)oxy]-3,3-diphenylpropionic Acid (12a). Compound **12a** was synthesized as described for **11h** using 2-(4-methoxyphenyl)ethanol in the first step: ^{1}H NMR (DMSO-d_6, 270 MHz) δ 7.4−7.1 (12 H, m), 6.7 (3 H, m), 6.2 (1 H, sbr), 4.0 (1 H, m), 3.7 (3 H, s), 3.65 (1 H, m), 2.8 (2 H, t), 2.3 (6 H, s); mp foam. HRMS calcd, 499.2231; found, 499.2210 $[M + H]^+$.

3-[2-(4-Chlorophenyl)ethoxy]-2-[(4,6-dimethylpyrimidin-2-yl)oxy]-3,3-diphenylpropionic Acid (12b). Compound **12b** was synthesized as described for **11h** using 2-(4-chlorophenyl)ethanol in the first step: ^{1}H NMR ($CDCl_3$, 200 MHz) δ 7.3−7.0 (14 H, m), 6.7 (1 H, s), 6.3 (1 H, s), 3.75 (1 H, m), 3.6 (1 H, m), 2.8 (2 H, m), 2.3 (6 H, s); mp 108−110 °C. HRMS calcd, 503.1736; found, 503.1733 $[M + H]^+$.

3-[2-(4-Ethoxy-3-methoxyphenyl)ethoxy]-2-[(4,6-dimethylpyrimidin-2-yl)oxy]-3,3-diphenylpropionic Acid (12c). Compound **12c** was synthesized as described for **11h** using 2-(4-ethoxy-3-methoxyphenyl)ethanol in the first step: ^{1}H NMR (DMSO-d_6, 270 MHz) δ 7.4−7.1 (10 H, m), 6.9−6.65 (4 H, m), 6.2 (1 H, s), 4.1−3.9 (3 H, m), 3.7 (3 H, s), 3.6 (1 H, m), 2.8 (2 H, t), 2.3 (6 H, s), 1.3 (3 H, t); mp 123−125 °C (dec). Anal. ($C_{32}H_{34}N_2O_6$) H, N; C: calcd, 72.2; found, 71.7. HRMS calcd, 543.2493; found, 543.2494 $[M + H]^+$.

3-(2-Phenylethoxy)-2-[(4,6-dimethylpyrimidin-2-yl)-oxy]-3,3-diphenylpropionic Acid (12d). Compound **12d** was synthesized as described for **11h** using 2-phenylethanol in the first step: ^{1}H NMR ($CDCl_3$, 200 MHz) δ 7.3 (15 H, m), 6.7 (1 H, s), 6.3 (1 H, s), 3.8 (1 H, m), 3.6 (1 H, m), 2.9 (2 H, t), 2.3 (6 H, s); mp 130−133 °C. HRMS calcd, 469.2126; found, 469.2120 $[M + H]^+$.

3-[2-(4-Hydroxyphenyl)ethoxy]-2-[(4,6-dimethylpyrimidin-2-yl)oxy]-3,3-diphenylpropionic Acid (12e). Compound **12e** was synthesized as described for **11h** using 2-(4-benzyloxyphenyl)ethanol in the first step. Deprotection of the hydroxy group was carried out as last step via catalytic hydrogenation (palladium on charcoal in ethyl acetate): ^{1}H NMR ($CDCl_3$, 270 MHz) δ 7.35−7.15 (10 H, m), 6.9 (2 H, d), 6.7 (1 H, s), 6.6 (2 H, d), 6.3 (1 H, s), 3.75 (1 H, m), 3.6 (1 H, m), 2.8 (2 H, t), 2.3 (6 H, s); mp 126−127 °C (dec). HRMS calcd, 485.2075; found, 485.2071 $[M + H]^+$.

3-[2-(4-Carboxymethoxy-3-methoxyphenyl)ethoxy]-2-[(4,6-dimethylpyrimidin-2-yl)oxy]-3,3-diphenylpropionic Acid (12f). Compound **12f** was synthesized as described for **11h** using 2-(3-methoxy-4-methoxycarbonylmethoxyphenyl)ethanol in step (a). Deprotection of the methyl ester was carried out during step (b) allowing a trianion during the last step: ^{1}H NMR (DMSO-d_6, 200 MHz) δ 7.3−7.1 (10 H, m), 6.9−6.6 (4 H, m), 6.1 (1 H, s), 4.5 (1 H, s), 4.0 (1 H, m), 3.8 (3 H, s), 3.7 (1 H, m), 2.8 (2 H, t), 2.3 (6 H, s); mp foam. HRMS calcd, 573.2235; found, 573.2225 $[M + H]^+$.

3-[2-(4-Carboxyphenyl)ethoxy]-2-[(4,6-dimethylpyrimidin-2-yl)oxy]-3,3-diphenylpropionic Acid (12g). Compound **12g** was synthesized as described for **11h** using 2-(4-carboxyphenyl)ethanol in step (a), allowing a trianion during the last step: ^{1}H NMR ($CDCl_3$, 200 MHz) δ 7.9 (2 H, d), 7.4 (2 H, d), 7.3−7.1 (10 H, m), 6.6 (1 H, m), 6.2 (1 H, s), 4.2 (1 H, m), 3.9 (1 H, m), 2.8 (2 H, m), 2.3 (6 H, s); mp foam. HRMS calcd, 513.2024; found, 513.2005 $[M + H]^+$.

3-[2-(4-Methoxyphenyl)ethoxy]-2-[(4-methoxy-6-methylpyrimidin-2-yl)oxy]-3,3-diphenylpropionic Acid (13a). Compound **13a** was synthesized as described for **11h** using using 2-(4-methoxyphenyl)ethanol in step (a) and 2-(methylsulfonyl)-4-methoxy-6-methylpyrimidine in step (c): ^{1}H NMR (DMSO-d_6, 270 MHz) δ 7.4−7.1 (12 H, m), 6.8 (2 H, d), 6.4 (1 H, s), 6.1 (1 H, s), 4.0 (1 H, m), 3.8 (3 H, s), 3.7 (3 H, s), 3.65 (1 H, m), 2.8 (2 H, t), 2.2 (3 H, s); mp foam. HRMS calcd, 515.2180; found, 515.2162 $[M + H]^+$.

3-[2-(4-Methoxyphenyl)ethoxy]-2-[(4-methoxy-5,6-dihydrofuro[2,3-*d*]pyrimidin-2-yl)oxy]-3,3-bis(4-methylphenyl)propionic Acid (13b). Compound **13b** was synthesized as described for **11h** using 2-(4-methoxyphenyl)ethanol and 3,3-bis-(4-methylphenyl)oxirane-2-carboxylic acid methyl ester[19] during step (a) and 2-(methylsulfonyl)-4-methoxy-5,6-dihydrofuro[2,3-*d*]pyrimidine in step (c): ^{1}H NMR (DMSO-d_6, 200 MHz) δ 7.3−7.0 (10 H, m), 6.8 (2 H, d), 6.0 (1 H, s), 4.6 (2 H, t), 3.8 (3 H, s), 3.75 (1 H, m), 3.65 (1 H, s), 3.5 (1 H, m), 3.0 (2 H, t), 2.8 (2 H, t), 2.2 (6 H, s); mp foam. HRMS calcd, 571.2442; found, 571.2462 $[M + H]^+$.

3-[2-(4-Methoxyphenyl)ethoxy]-2-[(4,6-dimethylpyrimidin-2-yl)oxy]-3,3-bis-(4-ethylphenyl)propionic Acid (13c). Compound **13c** was synthesized as described for **11h** using 2-(4-methoxyphenyl)ethanol and 3,3-bis-(4-ethylphenyl)oxirane-2-carboxylic acid methyl ester[19] during step (a): ^{1}H NMR ($CDCl_3$, 200 MHz) δ 7.3−7.0 (10 H, m), 6.8 (2 H, d), 6.6 (1 H, s), 6.3 (1 H, s), 3.75 (3 H, s), 3.6 (1 H, m), 3.45 (1 H, m), 2.8 (2 H, t), 2.6 (4 H, m), 2.3 (6 H, s), 1.2 (6 H, m); mp 130−133 °C (dec). HRMS calcd, 555.2857; found, 555.2865 $[M + H]^+$. Anal. ($C_{34}H_{38}N_2O_5$) C, H, N.

3-[2-(4-Methoxyphenyl)ethoxy]-2-[(4-methoxy-6-methylpyrimidin-2-yl)oxy]-3,3-bis-(4-ethylphenyl)propionic Acid (13d). Compound **13d** was synthesized as described for **11h** using 2-(4-methoxyphenyl)ethanol and 3,3-bis-(4-ethylphenyl)oxirane-2-carboxylic acid methyl ester during step (a) and 2-(methylsulfonyl)-4-methoxy-6-methylpyrimidine in step (c): ^{1}H NMR ($CDCl_3$, 200 MHz) δ 7.3−7.0 (10 H, m), 6.8 (2 H, d), 6.3 (1 H, s), 6.25 (1 H, s), 3.85 (3 H, s), 3.75 (3 H, s), 3.6 (1 H, m), 3.45 (1 H, m), 2.8 (2 H, t), 2.6 (4 H, m), 2.3 (3 H, s), 1.2 (6 H, m); mp 151−155 °C. HRMS calcd, 571.2806; found, 501.2811 $[M + H]^+$. Anal. ($C_{34}H_{38}N_2O_6$) C, H, N.

3-[2-(3,4-Dimethoxyphenyl)ethoxy]-2-[(4-methoxy-6-methylpyrimidin-2-yl)oxy]-3,3-diphenylpropionic Acid (13e). Compound **13e** was synthesized as described for **11h** using 2-(methylsulfonyl)-4-methoxy-6-methylpyrimidine in step (c): ^{1}H NMR ($CDCl_3$, 200 MHz) δ 7.3 (10 H, m), 6.7 (3 H, m), 6.2 (1 H, s), 6.18 (1 H, s), 3.9 (9 H, m), 3.8 (1 H, m), 3.6 (1 H, m), 2.8 (2 H, tr), 2.3 (3 H, s); mass spectra 545 $(M + H)^+$; mp foam.

3-[2-(3,4-Dimethoxyphenyl)ethoxy]-2-[(4-methoxy-6-methylpyrimidin-2-yl)oxy]-3,3-bis-(4-chlorophenyl)propionic Acid (13f). Compound **13f** was synthesized as described for **11h** using 3,3-bis-(4-chlorophenyl)oxirane-2-carboxylic acid methyl ester during step (a) and 2-(methylsulfonyl)-4-methoxy-6-methylpyrimidine in step (c): ^{1}H NMR ($CDCl_3$, 200 MHz) δ 7.2 (8 H, m), 6.7 (3 H, m), 6.3 (1 H, s), 6.0

(1 H, s), 3.9 (6 H, s), 3.85 (3 H, s), 3.65 (2 H, m), 2.8 (2 H, m), 2.3 (3 H, s); mp foam. HRMS calcd, 613.1506; found, 613.1509 $[M + H]^+$.

3-[2-(3,4-Dimethoxyphenyl)ethoxy]-2-[(4-methoxy-6,7-dihydro-5*H*-cyclopentapyrimidin-2-yl)oxy]-3,3-bis-(4-chlorophenyl)propionic Acid (13g). Compound **13g** was synthesized as described for **11h** using 3,3-bis-(4-chlorophenyl)-oxirane-2-carboxylic acid methyl ester[19] during step (a) and 2-(methylsulfonyl)-4-methoxy-6,7-dihydro-5*H*-cyclopentapyrimidin in step (c): ^{1}H NMR ($CDCl_3$, 200 MHz) δ 7.2 (8 H, m), 6.7 (4 H, m), 6.0 (1 H, s), 3.9 (3 H, s), 3.85 (3 H, s), 3.8 (3 H, s), 3.7 (2 H, m), 2.8 (6 H, m), 2.1 (2 H, quin); mp foam. HRMS calcd, 639.1663; found, 639.1653 $[M + H]^+$. Anal. ($C_{33}H_{32}Cl_2N_2O_7$) C, H, N.

3-[2-(3,4-Dimethoxyphenyl)ethoxy]-2-[(4-methoxy-6-methylpyrimidin-2-yl)oxy]-3,3-bis-(4-ethylphenyl)propionic Acid (13h). Compound **13h** was synthesized as described for **11h** using 3,3-bis-(4-ethylphenyl)oxirane-2-carboxylic acid methyl ester during step (a) and 2-(methylsulfonyl)-4-methoxy-6-methylpyrimidine in step (c): ^{1}H NMR ($CDCl_3$, 200 MHz) δ 7.0–7.4 (8 H, m), 6.6 (3 H, m), 6.25 (1 H, s), 6.2 (1 H, s), 3.8 (9 H, m), 3.7 (1 H, m), 3.45 (1 H, m), 2.75 (2 H, tr), 2.6 (4 H, m), 2.3 (3 H, s), 1.2 (6 H, m); mp foam. HRMS calcd, 601.2911; found, 601.2914 $[M + H]^+$.

(*S*)-2-Hydroxy-3-methoxy-3,3-diphenylpropionic Acid ((*S*)-7). A solution of sodium methoxide (44.6 g; 826 mmol) in methanol (130 mL) was added dropwise to a solution of L-proline methyl ester hydrochloride (137 g, 826 mmol) in methanol (130 mL) at room temperature, followed by the addition of methyl *tert*-butyl ether (2.4 L) and 3-methoxy-2-hydroxy-3,3-diphenylpropionic acid[19] (225 g; 826 mmol). The resulting mixture was heated in order to distill off a mixture of methanol and methyl *tert*-butyl ether (2.68 L) whereas methyl *tert*-butyl ether (2.4 L) was added simultaneously. During subsequent cooling to room temperature, (*R*)-3-methoxy-2-hydroxy-3,3-diphenylpropionic acid·L-proline methyl ester precipitated. The crystals, containing the not-desired enantiomer (*R*)-7, were separated by filtration and washed with methyl *tert*-butyl ether (150 mL). The mother liquor was concentrated by distilling off methyl *tert*-butyl ether (1.5 L), after which water (1.0 L) was added and the mixture was acidified to pH 1.2 by treatment with concentrated hydrochloric acid. After the mixture was stirred and the organic layer was separated, the aqueous layer was extracted again with methyl *tert*-butyl ether (400 mL). The organic layers were combined, washed with water (400 mL), and evaporated. The residue was dissolved in refluxing toluene, and the desired enantiomer was crystallized by slowly cooling to room temperature and by the addition of seeding crystals. Separation from the mother liquor by suction, washing with toluene, and drying in vacuo yielded (*S*)-2-hydroxy-3-methoxy-3,3-diphenylpropionic acid (78.7 g, 35% yield corresponding to the racemic mixture employed). Optical purity: 100% (chiral HPLC); chemical purity: 99.8% (HPLC).

(*S*)-2-Hydroxy-3-methoxy-3,3-diphenylpropionic Acid Methyl Ester ((*S*)-8). Sodium methoxide (10.8 g; 200 mmol) and (*S*)-2-hydroxy-3-methoxy-3,3-diphenylpropionic acid (54.4 g; 200 mmol) were suspended in DMF (300 mL). The resulting slurry was treated dropwise with dimethyl sulfate (21.0 mL; 210 mmol) over a period of 15 min during which the mixture warmed to 50 °C and became less viscous. The mixture was stirred overnight and poured into water/ice (1.5 L), followed by extraction with ether (2 × 500 mL). The combined organic layers were washed with water (2 × 200 mL), dried over magnesium sulfate, and evaporated. The resulting crude oil (55.8 g) was used without further purification.

(*S*)-3-[2-(3,4-Dimethoxyphenyl)ethoxy]-2-hydroxy-3,3-diphenylpropionic Acid Methyl Ester ((*S*)-9). (*S*)-2-Hydroxy-3-methoxy-3,3-diphenylpropionic acid methyl ester (27.9 g; 100 mmol), *p*-toluenesulfonic acid (1 g), and 2-(3,4-dimethoxyphenyl)ethanol (18.2 g; 100 mmol) were dissolved in dichloromethane (75 mL). The resulting solution was heated in order to distill off the solvent and methanol generated by the transetherification of the starting material; dichloromethane was replaced simultaneously to ensure a continuous removal of methanol. This procedure was performed for 5 h at a bath temperature of 60 °C after which the reaction mixture was cooled to room temperature and diluted with ether (300 mL). The resulting solution was washed with aqueous sodium bicarbonate and then, repeatedly, with water. The organic layer was dried over magnesium sulfate and evaporated to yield an oily residue (43 g), which was used without further purification.

(*S*)-3-[2-(3,4-Dimethoxyphenyl)ethoxy]-2-hydroxy-3,3-diphenylpropionic Acid ((*S*)-10). Compound (*S*)-**10** was synthesized from (*S*)-**9** by ester hydrolysis as described for compound **11h** in step (b): yield 60% starting from (*S*)-**8**; $[\alpha]^{20} = +25.4$ ($c = 1$; methanol).

(*S*)-3-[2-(3,4-Dimethoxyphenyl)ethoxy]-2-(4,6-dimethylpyrimidin-2-yloxy)-3,3-diphenylpropionic Acid ((*S*)-11h). Compound (*S*)-**11h** was synthesized from (*S*)-**10** as described for compound **11h** in step (c): $[\alpha]^{20} = +122.3$ ($c = 1$; methanol). Anal. ($C_{31}H_{32}N_2O_6$) C, H, N.

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